Int. Soc. Opt. Eng. pp. 340-347), Kajiwara (1990, JP 02111747), and Jaffe et al (1990, Biochemistry, pp. 8345-50).

The references will be referred to as Kennedy, Jichlinski, Kajiwara and Jaffe, respectively.

The Examiner's position is set forth in the Action in detail and Applicants will not repeat the Examiner's language here except as necessary to an understanding of Applicants' traversal which is now presented.

The Examiner seems to be making four main points in the Action, and Applicants discuss these and respond to these below.

Point 1

The first argument that the Examiner addresses is the argument that the present invention is drawn to a method of administering isotope ALA to the living body of the subject and conducting a biochemical reaction, whereafter malignant tumors are detected by the distribution of the isotope without any separation of the compound. See, for example, Response, page 6, second full paragraph.

The Examiner responds that this argument is not persuasive because:

Jichlinski teaches administering labeled 5-ALA to the living body of a subject and the same being subjected therein to a biochemical reaction to detect malignant tumors.

Applicants' Response:

In Jichlinski, 5-ALA is administered to the living body, and protoporphyrine IX synthesized from 5-ALA in the living body and accumulated in tumors is photodetected by

fluorescence to thereby detect malignant tumors. Jichlinski does not teach that isotope-labeled 5-ALA is administered to the living body to thereby detect malignant tumors.

The Examiner than reads Jaffe as teaching detailed NMR techniques for detecting the biochemical product in the living body of a subject who received 5-ALA. The Examiner appears to be suggesting that Jaffe in fact deals with *in vivo* studies

With respect to Kajiwara, the Examiner reads Kajiwara as teaching radiolabeled 5-ALA is useful for diagnosis.

Applicants' Response:

Applicants treat Jaffe and Kajiwara together.

In Jaffe and Kajiwara, isotope-labeled 5-ALA is administered to a living body to undergo biochemical reaction in the living body. Synthesized porphobilinogen (PBG) is then separated by extraction, and the position of the isotope is analyzed by NMR to thereby clarify the function of ALA dehydratase which produces PBG. Therefore, in Jaffe and Kajiwara, NMR is not used for the detection of 5-ALA in the living body. Furthermore, the analysis of the position of the isotope is carried out for PBG purified *in vitro*, so that *in vivo* experiments are not carried out in Jaffe and Kajiwara.

Furthermore, Kajiwara only discloses that PBG is useful as a therapeutic drug for lead poisoning, but does not disclose diagnosis of malignant tumors (see page 5, lines 22-23 in the English translation). Kajiwara also does not teach the administration of 5-ALA into the living body.

Point 2

In the last full paragraph on page 2 of the Action, the Examiner specifically takes the position that the amount of isotope label is not measured in a living body, rather, is measured outside a living body using the same NMR techniques taught in Jaffe. The Examiner cites the specification at pages 25-26 and the NMR data in Fig. 1 to support this conclusion.

Applicants' Response:

Applicants respectfully submit that to one of ordinary skill in the art quite clearly in accordance with the claims of the present application the amount of isotope labeled by necessity is measured in a living body.

From a technical viewpoint, the Examiner is also believed to be incorrect. When MRI, which is a type of NMR is used, the amount of isotope level would be measured in a living body. Also, an NMR stethoscope of high sensitivity would be expected to be used for the measurement, which would correlate with measurement in the human body.

Point 3

In the first full paragraph on page 3 of the Action, it is believed the Examiner addresses the argument made in the first full paragraph on page 6 of the Response that in Kennedy light exposure is essential for detection of malignant tumors and "wet" operations are necessary whereas in accordance with the present invention, diagnosis can be carried out by what might be considered "low wet" operations involving a combination of an isotope and NMR or MRI.

In any case, assuming that the Examiner is correct, in Response at page 6, first full paragraph, simply changing "detection" to --destruction-- would certainly be accurate. With respect to the Examiner's statement that the claims do not say anything about operations

involving a combination of an isotope and NMR or MRI, Applicants request a telephone interview on this point, especially considering the Examiner's statement that the specification does not teach anything about operations involving a combination of an isotope and NMR or MRI.

Applicants' Response:

If the Examiner would find claim 10 amended as follows to reflect allowable subject matter, the Examiner is requested to contact the undersigned. In any case, the undersigned will be calling the Examiner in the next few days to see if a telephone interview can be arranged concerning this application.

Proposed Amendment to Claim 10

10. A method for detecting and treating malignant tumors, which method comprises;

administering a tumor detecting effective amount, to a host in need of detection of a malignant tumor, a 5-aminolevulinic acid or a derivative thereof in which at least one carbon atom of said 5-aminolevulinic acid is a carbon isotope and/or a nitrogen atom in its amino group is a nitrogen isotope, and where said derivative is an ester, amide, salt, hydrate or solvate of said 5-aminolevulinic acid to thereby accumulate the carbon isotope and/or the nitrogen isotope in the malignant tumor;

detecting the ~~malignant tumor~~ carbon and/or the nitrogen isotope using NMR to thereby identity the position of the malignant tumor; and

administering an effective amount of said 5- aminolevulinic acid or a derivative thereof, in which at least one carbon atom of said 5- aminolevulinic acid is a carbon isotope and/or a nitrogen atom in its amino group is a nitrogen isotope, and where said derivative is an ester, amide, salt, hydrate or solvate of said 5- aminolevulinic acid, to kill said malignant tumor.

If the Examiner feels that terminology such as detection in a living host or the like would be of assistance to reflect allowable subject matter, the Examiner is requested to contact the undersigned.

Point 4

Turning now to the second full paragraph on page 3 of the Action, the Examiner here addresses the lack of motivation arguments.

It was argued that Kennedy relates to a medical treatment technique, the remaining references relate to studies on metabolism by structural analysis and that these are quite different technical fields and the problems are not the same, essentially non-analogous art was argued in the sense that one of ordinary skill in the "medical art" (Kennedy) would not turn to metabolic studies (the remaining references), and vice-versa, and, thus, there is no motivation to combine the prior art since the prior art is non-analogous.

The Examiner does not seem to address the issue of lack of motivation explicitly, but presumably the Examiner's reasoning is basically that Kajiwara with Jichlinski teach administration of 5-ALA to a living body of a subject to detect the presence of cancer, Jaffe teaches details of NMR involving labeled 5-ALA, and these three references in total suggest that isotope labeled 5-ALA could be used in combination with NMR to detect cancer in a patient after administering the isotope labeled 5-ALA with a reasonable expectation of success.

The Examiner then continues and reasons that cancer diagnosis is mandatory before cancer treatment. Having found the secondary references to teach a method of diagnosing cancer using 5-ALA as claimed, the Examiner reasons that it would be obvious to then follow the

teaching of Kennedy and use the Kennedy method of cancer treatment using the same compound thus achieving detection and killing effects ("catching two birds with a single stone").

Applicants' Response:

First, with respect to Kajiwara, the Examiner states (Action, page 3, second full paragraph):

"...Kajiwara teaches isotope labeled 5-ALA could be useful for a diagnosis [of cancer]..."

Applicants respectfully submit that Kajiwara does not reasonably teach to one of ordinary skill in the art the diagnosis of malignant tumors, rather, only discloses the diagnosis of lead poisoning. Further, Kajiwara does not teach the administration of 5-ALA into a living body.

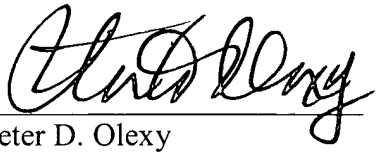
In accordance with the present invention, the position of malignant tumors is diagnosed by administering labeled 5-ALA into a living body and identifying the position of the labeled 5-ALA in the living body, without separating the 5-ALA. This aspect of the present invention is believed clearly novel and unobvious over the prior art relied upon. Thus, Applicants respectfully submit that this feature of the present invention is not reasonably suggested to one of ordinary skill in the art from the references cited, even if one were to be knowledgeable in the field of bioscience and the field of medicine.

Finally, on the issue of motivation, Applicants do not believe that one of ordinary skill in the field of the biosciences, active in the study of metabolism, would be led to apply that knowledge regarding metabolism to measurement of isotope levels in the living body.

Considering all of the above, withdrawn of the rejection and allowance is requested.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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